

NIH Consensus Statement

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Ovarian Cancer: Screening, Treatment, and Followup

NATIONAL INSTITUTES OF HEALTH
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This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.



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Abstract

Objective

To provide physicians with a current consensus on screening, prevention, diagnosis, and treatment of ovarian cancer.

Participants

A non-Federal, nonadvocate, 14-member consensus panel representing the fields of gynecologic, medical, and radiation oncology, obstetrics/gynecology, and biostatistics; 25 experts in obstetrics/gynecology and gynecologic, medical, and radiation oncology who presented data to the consensus panel; and a conference audience of approximately 500.

Evidence

The literature was searched through Medline and an extensive bibliography of references was produced for the panel and the conference audience. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given priority over clinical anecdotal experience.

Consensus

The panel, answering predefined consensus questions, developed their conclusions based on the scientific evidence presented in open forum and the scientific literature.

Consensus Statement

The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. The panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference.

Conclusions

There is no evidence available yet that the current screening modalities of CA 125 and transvaginal ultrasonography can be effectively used for widespread screening to reduce mortality from ovarian cancer nor that their use will result in decreased rather than increased morbidity and mortality. Women with stage IA grade 1 and IB grade 1 ovarian cancer do not require postoperative adjuvant therapy. Many remaining stage I patients do require chemotherapy. Subsets of stage I must be fully defined and ideal treatment determined. Women with stages II, III, and IV epithelial ovarian cancer (other than low malignant potential tumors) should receive postoperative chemotherapy.

Introduction

Ovarian cancer is the leading cause of death from gynecologic malignancies in the United States. In 1994, approximately 24,000 new cases of ovarian cancer will be diagnosed, and 13,600 women will die of the disease. Over the past several years, significant new information has been generated regarding the epidemiology, biology, risk reduction, screening, treatment, and followup of ovarian cancer.

On April 5 through 7, 1994, the National Cancer Institute, together with the Office of Medical Applications of Research of the National Institutes of Health, convened a Consensus Development Conference on Ovarian Cancer: Screening, Treatment, and Followup. The purpose of this conference was to identify the issues for which there are currently sufficient confirmed data, so that health care providers will have these data available to them and so that all women can benefit from this information. Secondly, for issues that are important but for which there are not sufficient data, the panel was charged with recommending directions for important avenues of future research.

At the consensus conference, members of an independent, non-Federal, scientific panel with public and patient representation heard and discussed the current data pertinent to these issues. The panel then weighed the scientific evidence and drafted answers to the following key questions:

- What is the current status of screening and prevention of ovarian cancer?
- What is the appropriate management of early-stage ovarian cancer?
- What is the appropriate management of advanced epithelial ovarian cancer?
- What is appropriate followup after primary therapy?
- What are important directions for future research?

What Is the Current Status of Screening and Prevention of Ovarian Cancer?

Introduction

Recent events have brought ovarian cancer under close scrutiny in the lay press and have increased demand for early detection of this devastating disease. The survival rate of women with early-stage ovarian cancer is significantly higher than that of women with advanced-stage disease. Unfortunately, the vast majority of women with ovarian cancer are diagnosed with advanced disease. Although sometimes women with early ovarian cancer have symptoms such as vague gastrointestinal discomfort, pelvic pressure, and pain, more often women with early ovarian cancer have no symptoms, or very mild and nonspecific symptoms. By the time symptoms are present, women with ovarian cancer usually have advanced disease.

The advent of the CA 125 serum tumor marker and improvements in pelvic ultrasound, along with newer techniques of color Doppler imaging (CDI) studies of ovarian vessels, have led some to advocate the use of these modalities in the attempt to detect early-stage ovarian cancer. To place the disease in perspective, its prevalence is 30–50/100,000, with the lifetime incidence being 1 in 70 women.

Risk Factors

Although the cause is unknown, some women are at higher risk of developing ovarian cancer than others. Risk factors include advancing age; nulliparity; North American or Northern European descent; a personal history of endometrial, colon, or breast cancer; and a family history of ovarian cancer. The evidence is inconsistent regarding the use of fertility drugs as a risk factor. Less than 0.05 percent of women are at significantly increased risk because of cancer syndrome; site-specific ovarian cancer syndrome; and hereditary nonpolyposis colorectal cancer or Lynch syndrome II, which includes early-onset nonpolyposis colorectal cancer, endometrial cancer, cancer of

the upper gastrointestinal system (including biliary ducts, pancreas, and possibly small bowel), urothelial carcinomas of the renal pelvis and ureter, and ovarian cancer.

Screening for Ovarian Cancer

To be suitable for screening, a disease must have a significant prevalence and be a significant cause of mortality. There must be a preclinical phase that can be detected, and the disease must be amenable to therapy. The screening test itself must have sufficient specificity, sensitivity, and positive predictive value (PPV) to be effective, and it must be cost-effective. In ovarian cancer, if one assumes a prevalence of 50/100,000, a test with 99 percent specificity and 100 percent sensitivity would yield only 1 in 21 women with a positive screen actually having the disease (i.e., PPV = 4.8 percent). It must be noted that currently available tests do not attain the aforementioned high level of sensitivity.

Three screening tests are in general use: bimanual rectovaginal pelvic examination, CA 125, and transvaginal ultrasonography (TVS). CDI is also being investigated in some centers regarding its role as an adjunct to TVS. Historically, rectovaginal pelvic examination has been the only method used to detect ovarian cancer at any stage. Although pelvic exam is an important part of routine gynecologic care, it has inadequate sensitivity and specificity as a screening test for ovarian cancer.

CA 125 is an antigenic determinant detected by radio-immunoassay. It is elevated in 80 percent of epithelial ovarian cancers. However, only half of the patients with stage I cancers have elevated levels. Because detecting early disease is the goal of screening, CA 125 alone is not an adequate screening test. In addition, a significant proportion of healthy women and women with benign disease have elevations in CA 125 resulting in an unacceptably low specificity for this test.

Transabdominal ultrasound and TVS have been studied as noninvasive screening tools. TVS is currently the preferred

modality. However, specificity of ultrasonography is not adequate for use as a single screening modality. For example, in a representative study, 5,479 women, 96 percent of whom were 45 years of age or older, were screened using abdominal ultrasound, and there were 338 positive screens. This resulted in exploratory laparotomy in 326 women, and five stage I ovarian cancers were found. Three had borderline histology, and, therefore, diagnosis at a later date may not have affected survival. Sixty-five laparotomies were performed for each case of ovarian cancer detected. In a similar screening study of women with a family history of ovarian cancer, 1,601 pre- and postmenopausal women were screened using TVS. Sixty-one operations detected five stage I ovarian cancers, three of which were of borderline histology. The combination of CA 125 screening and TVS significantly improves the specificity of screening and has reduced the proportion of women requiring unnecessary surgical intervention. However, there is a potential for significant anxiety related to abnormal screening test results as well as morbidity and even mortality from resultant surgical procedures in women with no significant pathology, which may outweigh any potential benefits.

Recommendations for Screening

All women should have a comprehensive family history taken by a physician knowledgeable in the risks associated with ovarian cancer and should continue to undergo annual rectovaginal pelvic examination as part of routine medical care. The lifetime risk of ovarian cancer in a woman with no affected relatives is 1 in 70, and in a woman with one first-degree relative with ovarian cancer is 5 percent. With current knowledge and technology, the benefits of screening a woman who has one or no first-degree relatives with ovarian cancer are unproven. The risks may outweigh the benefits, particularly in women with no family history or other high risk factors. There is currently no evidence to support routine screening in these women. However, participation in clinical screening trials is an appropriate option, and is important in helping to ultimately define the potential benefits and risks of screening. If a woman has one first-degree relative with

ovarian cancer (making her lifetime risk of developing the disease 5 percent) but no clinical trials are available to her, she may feel that despite the absence of prospective data, this is sufficient risk for her to be screened. This alternative and opportunity should be available to the woman and her physician.

With two or more first-degree relatives, a woman's lifetime risk rises to 7 percent. There are no conclusive data that screening benefits these women. However, women with two or more family members affected by ovarian cancer have a 3 percent chance of having a hereditary ovarian cancer syndrome and should be counseled by a gynecologic oncologist or other qualified specialist regarding their individual risk.

For patients with a hereditary ovarian cancer syndrome (assuming autosomal dominant inheritance with 80 percent penetrance), the lifetime risk of ovarian cancer is approximately 40 percent. There are no data demonstrating that screening these high-risk women reduces their mortality from ovarian cancer. Nonetheless, at least annual rectovaginal pelvic examination, CA 125 determinations, and TVS are recommended in these women. When childbearing is completed, or at least by age 35, prophylactic bilateral oophorectomy is recommended to reduce this significant risk. Prophylactic oophorectomy does not preclude a small risk of developing peritoneal carcinomatosis, which is clinically similar to advanced ovarian cancer.

Protective Factors and Prophylactic Bilateral Oophorectomy

Clearly established protective factors include greater than one full-term pregnancy, oral contraceptive use, and breastfeeding, all of which reduce incessant ovulation. Tubal ligation has also been described as a possible protective factor. The risk reduction associated with greater than 5 years of oral contraceptive use is estimated in one study to be 37 percent. Relatively short duration of use may be beneficial, but prolonged use appears to extend this benefit.

A woman with one first-degree relative with ovarian cancer has a lifetime risk of ovarian cancer of 5 percent. This is probably not high enough to warrant prophylactic oophorectomy as an independent operative procedure with its attendant risks. The probability of a hereditary ovarian cancer syndrome in a family pedigree increases with the number of affected relatives, with the number of affected generations, and with young age of onset of disease. Therefore, prophylactic oophorectomy should be considered in these settings with careful weighing of the risks and potential benefits. The risk of ovarian cancer in women from families with hereditary ovarian cancer syndromes (as discussed above) is sufficiently high to recommend prophylactic oophorectomy in these women at age 35 or after childbearing is completed.

Prophylactic oophorectomy performed in women undergoing abdominal surgery for other indications such as benign uterine disease is also associated with a significant reduction in the risk of ovarian cancer. However, estrogen replacement therapy should be discussed with the patient prior to the procedure.

Although prophylactic oophorectomy lowers the risk of ovarian cancer in both pre- and postmenopausal women, noncompliance with estrogen replacement therapy may result in a significant reduction in life expectancy due to cardiovascular disease and osteoporosis in premenopausal women who have bilateral oophorectomy, compared with women with retained ovaries. Therefore, premenopausal women who cannot comply with estrogen replacement therapy should be advised regarding these risks as well as the benefits of prophylactic oophorectomy.

What Is the Appropriate Management of Early-Stage Ovarian Cancer?

Management of the Adnexal Mass

It is estimated that 5 to 10 percent of women in the United States will undergo a surgical procedure for a suspected ovarian neoplasm during their lifetime, and 13 to 21 percent of these women will be found to have an ovarian malignancy. Since the majority of adnexal masses are benign, it is important to try to determine preoperatively whether a patient is at high risk for ovarian malignancy, in order to ensure proper management.

To determine whether an adnexal mass requires surgery, and what the appropriate preparation and intervention should be, preoperative evaluation must include a complete history and physical examination (including bimanual and rectovaginal examination). TVS examination can help to further evaluate a suspected ovarian mass. CA 125 may aid in the evaluation in postmenopausal women, but can confound it in premenopausal women because of the many benign conditions associated with an elevated serum CA 125 level.

Once an adnexal mass has been documented, management depends upon a combination of many predictive factors including

1. Age and menopausal status
2. Size of the mass
3. Ultrasonographic features
4. Presence or absence of symptoms
5. Level of CA 125
6. Unilaterality versus bilaterality.

A woman's age is an important factor in predicting whether an ovarian mass is malignant. Despite the fact that ovarian cancer is more common in older women, it occurs in young women as well. In premenopausal, asymptomatic women

with simple cystic adnexal masses less than 6–10 cm, expectant management is a reasonable approach, since 70 percent of these masses will resolve without therapy. The common practice of ovarian suppression with oral contraceptives in these women is unproven. Expectant management should include a repeat physical and pelvic examination and TVS. Changes in clinical or ultrasonographic findings to those more characteristic of malignancy, or persistence of a significant mass, are indications for surgery. Most ovarian masses in postmenopausal women will require surgical evaluation. The possible exception may be in those women with a subclinical cyst detected on ultrasound, which is unilocular, less than 5 cm in diameter, and associated with normal serum CA 125 levels. Although a variety of clinical and laboratory parameters are extremely useful in both pre- and postmenopausal women, no combination of factors can be considered 100 percent accurate in predicting malignancy.

Surgical Therapy

Once surgical removal is indicated, the question of which surgical approach to use (laparoscopy versus laparotomy) must be addressed. Large numbers of laparoscopic procedures are being performed in this country for adnexal masses. However, data are lacking as to the efficacy and safety of this approach in the management of possible ovarian malignancy. If an unsuspected ovarian malignancy is detected at the time of diagnostic laparoscopy, staging and debulking by laparotomy should be undertaken without delay, and is ideally performed by a gynecologic oncologist.

Management of Early-Stage Epithelial Ovarian Cancer (Stage I)

Approximately 25 percent of women with newly diagnosed ovarian cancer present with stage I disease (see Table 1). Outcomes for these women are much better than those of their counterparts with advanced-stage disease. Nevertheless, a significant proportion of women with stage I disease die from their malignancies. Much attention has been focused

Table 1**FIGO (1986) Staging System for Ovarian Cancer**

Stage	Characteristic
I	Growth limited to the ovaries
IA	Growth limited to one ovary; no ascites; no tumor on the external surfaces, capsule intact
IB	Growth limited to both ovaries; no ascites; no tumor on the external surfaces, capsule intact
IC	Tumor either stage IA or stage IB but with tumor on the surface of one or both ovaries, or with capsule ruptured, or with ascites containing malignant cells, or with positive peritoneal washings
II	Growth involving one or both ovaries on pelvic extension
IIA	Extension or metastases to the uterus or tubes
IIB	Extension to other pelvic tissues
IIC	Tumor either stage IIA or IIB with tumor on the surface of one or both ovaries, or with capsule(s) ruptured, or with ascites containing malignant cells, or with positive peritoneal washings
III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes; superficial liver metastases equals stage III; tumor is limited to the true pelvis but with histologically verified malignant extension to small bowel or omentum
IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIB	Tumor of one or both ovaries; histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes negative
IIIC	Abdominal implants greater than 2 cm in diameter or positive retroperitoneal or inguinal nodes
IV	Growth involving one or both ovaries with distant metastases; if pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV; parenchymal liver metastases equals stage IV

Staging Announcement: FIGO Cancer Committee. *Gynecol Oncol* 25:383, 1986.

on identifying the subsets of women at highest risk of relapse who may benefit from adjuvant therapy. Precise definition of these subsets on the basis of surgical findings and histologic grade is not agreed upon. However, the following recommendations are made based on existing data:

1. Patients with stage IA grade 1 and most IB grade 1 tumors do not require adjuvant therapy.
2. All patients with grade 3 tumors require adjuvant therapy.
3. Patients with clear cell carcinoma require adjuvant therapy.
4. Many but not all women with stage IC disease require adjuvant therapy.
5. Consensus on the need for postoperative adjuvant therapy in the remaining subsets of patients with stage I epithelial ovarian cancer could not be reached.

6. Although it is clearly acknowledged that many subsets of women with stage I ovarian cancer have a substantial likelihood for recurrence and mortality, the most effective adjuvant therapy has not been established. Ideally, patients with these high-risk stage I cancers should be enrolled in clinical trials to identify adjuvant therapy that will optimally improve survival.

All women who have ovarian cancer should have meticulously performed surgical staging. Most women who have stage I ovarian cancer will have a total abdominal hysterectomy/bilateral salpingo-oophorectomy (TAH/BSO). However, since some of these women are young and are interested in maintaining reproductive capability, after complete surgical staging has been done there is an option to preserve their reproductive potential. For instance, some young women with stage IA tumors may be able to have the option of preservation of the uterus and contralateral adnexa, and some young women with stage IB tumors may have preservation of the uterus.

Low Malignant Potential Tumors

The recommended treatment for patients with low malignant potential (LMP) ovarian tumors who have completed child-bearing is TAH/BSO and optimal staging and debulking. There is no evidence that adjuvant therapy improves disease-free survival or overall survival in these women. Although no prospective study has compared the efficacy of TAH/BSO with more conservative therapy in stage IA disease, data from retrospective studies of conservative therapy in young women suggest that the risk of recurrence is not significantly different than in patients treated with TAH/BSO.

Although repeat staging laparotomy may possibly result in upstaging in those patients who were incompletely staged at the time of their initial surgery, the therapeutic benefit of reexploration is of questionable value if no evidence of gross residual disease existed at the time of the initial surgery.

Germ Cell Cancers

Ovarian germ cell cancers account for less than 5 percent of all ovarian malignancies. They typically occur in girls and young women. Although no prospective randomized studies exist comparing unilateral with bilateral adnexectomy, retrospective analyses demonstrate equivalent cure rates with either surgical procedure, with or without hysterectomy. Since ovarian germ cell cancers are mostly unilateral, with the exception of dysgerminomas, it seems prudent to avoid biopsy of a normal-appearing contralateral ovary.

Complete surgical staging is necessary to determine the extent of disease and guide postoperative treatment, which most patients require. Current data indicate that the most active adjuvant chemotherapy for germ cell cancers of the ovary is the combination of bleomycin, etoposide, and cis-platinum.

Sex Cord Stromal Cancers

Sex cord stromal cancers are rare and are characterized by somewhat unpredictable biologic behavior. Most are unilateral and can be treated with adnexectomy and staging in young women. In women who have completed childbearing, surgical staging and TAH/BSO are appropriate. Optimal adjuvant therapy has not yet been determined.

Pathology

In cases of unusual histologic subtypes (e.g., LMP tumors), an additional independent review of the pathologic specimen should be sought.

What Is the Appropriate Management of Advanced Epithelial Ovarian Cancer?

Preoperative Evaluation

For the purpose of this report, anything other than stage I ovarian cancer represents advanced disease. Ovarian cancer is diagnosed at an advanced stage in approximately 75 percent of patients. The ability to accurately identify advanced-stage ovarian cancer preoperatively is of particular importance in the community setting since availability of appropriate technical expertise for staging and debulking may require additional preparation or referral. It is critical to avoid unnecessary delay of the primary surgical procedure. A careful history and physical examination, including bimanual rectovaginal pelvic examination, is the first step in patient evaluation. A chest x-ray is part of routine preoperative evaluation in patients suspected of having ovarian cancer. Extensive imaging studies often do not add valuable information to careful diagnostic ultrasound unless symptoms suggest particular organ involvement. CT scans, MRI's, IVP's, and barium enemas may have a role in preoperative evaluation, and this should be determined on a case by case basis. Ultrasound is well suited for evaluation of a pelvic mass and assessment of ascites. Sonographic features of pelvic masses are amenable to quantitative grading and have been shown in various studies to be helpful in predicting malignancy. CDI may enhance ultrasound specificity for predicting malignancy of an adnexal mass, but its use in this situation is investigational. CA 125 is elevated in approximately 80 percent of patients with ovarian cancer and is a useful reflection of disease status during and after therapy in those patients. Although not completely diagnostic, combining CA 125 with sonographic morphologic features and menopausal status may assist in assessing the potential for ovarian cancer.

In patients with suspected ovarian cancer, other preoperative studies should include assessment of hematologic, hepatic, and renal function. Preoperative bowel preparation should be utilized because the potential for bowel resection exists and is poorly predicted by available preoperative studies.

Prognostic Factors

Reproducible independent factors that prolong survival include younger age, early stage, low tumor grade, low residual tumor volume, and rapid rate of tumor response. Other prognostic factors include initial tumor volume and para-aortic lymph node involvement. A serum CA 125 level obtained 4 weeks after surgical debulking appears to be helpful; however, it may not be an independent prognostic factor.

Surgery

Adequate and complete surgical intervention is mandatory primary therapy for ovarian carcinoma, permitting precise staging, accurate diagnosis, and optimal cytoreduction. The procedure is best conducted by a qualified gynecologic oncologist when there is high probability of ovarian carcinoma. In situations when a mass is most probably benign, a qualified gynecologic surgeon can provide operative intervention. Consultative backup by a gynecologic oncologist may be advantageous.

The surgical procedure requires an adequate vertical incision, assessment of peritoneal fluid volume, and fluid cytology. For staging purposes, when a patient appears to have early disease, biopsies should be taken from the pelvic side walls, cul-de-sac, and paracolic gutters. The infradiaphragmatic surface should be evaluated by cytology or biopsy. Bowel serosa and mesentery should be evaluated for tumor. The infracolic omentum should be removed. Following biopsies, an extr fascial TAH/BSO should be completed. Pelvic and para-aortic lymph node sampling is a part of surgical staging. Aggressive efforts at maximal cytoreduction are important since minimal residual tumor is associated with improved survival.

In selected patients who have not had the opportunity for adequate staging and debulking at the time of initial surgery, a definitive operative procedure as previously described should be completed expeditiously before further therapy is undertaken. If it is impossible to achieve optimal debulking despite maximum effort, interval cytoreduction (surgery performed midway through a chemotherapy regimen) may play a role and is under investigation.

Second-look operations outside of clinical trials should only be undertaken if the anticipated findings will alter subsequent management. Given the fact that many patients with negative second-look laparotomies will develop recurrent cancer, protocols should be developed to evaluate the benefits of consolidation therapy in the context of clinical trials.

Chemotherapy

Systemic chemotherapy following the appropriate surgical procedure is the cornerstone of first-line treatment of advanced epithelial ovarian malignancy. Chemotherapy is most effective in patients who have undergone maximal cytoreductive surgery or who present with a low volume of disease. At the consensus conference, important new data from a randomized trial (in suboptimal stage III and IV) comparing a combination of cis-platinum and paclitaxel (administered over 24 hours) with a combination of cis-platinum and cyclophosphamide were presented and reviewed by the panel. Preliminary results strongly suggested superiority for the paclitaxel-based regimen. Based on these new data, some but not all clinicians and investigators consider the combination of platinum and paclitaxel the treatment of choice for advanced epithelial ovarian cancer. No consensus could be reached on unqualified endorsement of this recommendation pending the availability of long-term results from this trial. In addition, the optimal dose and schedule of paclitaxel is the subject of ongoing clinical trials.

Data from mature randomized clinical trials have indicated that the combination of carboplatin and cyclophosphamide is effective therapy. Other mature trials have shown equal activity for the combination of cis-platinum and cyclophosphamide, but the substitution of carboplatin leads to more acceptable toxicity. Six cycles of chemotherapy have become the standard and yield clinical response rates of approximately 60 to 70 percent and 5-year survivals of 10 to 20 percent.

Currently available data do not in general support the routine addition of doxorubicin to the combination of platinum compounds and cyclophosphamide. In the treatment of ovarian

cancer, hematologic toxicity is usually not of sufficient grade to warrant the routine use of hematopoietic growth factors when standard doses of chemotherapy are employed. In addition, high-dose chemotherapy with hematopoietic growth factors or bone marrow transplantation is experimental, and its use should be limited to research settings.

The role of intraperitoneal chemotherapy in the treatment of ovarian cancer remains to be defined.

Radiotherapy

The role of radiotherapy in advanced epithelial ovarian cancer is controversial. Long-term, relapse-free survivals have been demonstrated for stages II and III after optimal debulking and postoperative radiotherapy. No recent prospective trials of whole abdominal irradiation compared with chemotherapy have been performed.

What Is the Appropriate Followup After Primary Therapy?

The ideal followup of asymptomatic women who have completed primary debulking surgery and chemotherapy and have no clinical evidence of disease is unclear. Second-look laparotomy has been used to assess response to therapy. As indicated above, the role of this procedure is controversial. The followup of asymptomatic patients after primary therapy should include routine complete history, physical, rectovaginal pelvic exam, and CA 125. Although optimal intervals for monitoring have not been determined, current practice is to follow the patient every 3 to 4 months. After 2 years, less frequent followup intervals can be considered. CA 125 has been shown to be a reliable method of monitoring for early detection of recurrence in women whose CA 125 was elevated preoperatively. A rising CA 125 is a predictor of relapse; however, a negative CA 125 does not exclude the presence of disease. A combination of CA 125 and general physical and pelvic exam has been shown to detect progression of disease in 90 percent of patients with recurrent epithelial ovarian cancer. Radiological exams done on a routine basis have not been shown to improve the detection of recurrence. Their use should be individualized.

Management of Patients at Relapse

In the overwhelming majority of patients who relapse, presently available salvage therapy for ovarian cancer is not curative. Therefore, the goals of followup and treatment of relapsed patients need to incorporate quality of life considerations as an integral part of treatment. Patients who have relapsed after primary chemotherapy with platinum can be divided into two groups based on interval to relapse. Patients who relapse within 6 months have a poor subsequent response to platinum-containing regimens. Those who relapse after 6 months have a higher likelihood of response to platinum-containing regimens. Paclitaxel is currently the most active single agent for treatment of relapsed ovarian cancer even in patients

refractory to platinum. It has an overall response rate of approximately 35 percent. Despite this response rate, there is no evidence yet that this salvage therapy prolongs survival.

Repeat surgical debulking in relapsed patients will probably only benefit a small subset of highly selected patients. These include patients with a long disease-free survival interval (greater than 2 years) who had optimal primary debulking surgery. However, surgery may be important for palliation, such as for the treatment of bowel obstruction in a patient whose quality of life stands to benefit from this intervention. Radiation therapy may be used for the palliation of specific localized symptoms.

When a patient relapses for the second time, there is almost no possibility of cure. Temporary response rates of approximately 15 percent have been achieved by several different chemotherapeutic regimens. After paclitaxel and platinum compounds are no longer effective, agents that may produce response include ifosfamide, hexamethylmelamine, tamoxifen, 5-FU, etoposide, and others. No survival benefit has been demonstrated by any of these regimens.

Given the rigors of chemotherapy, patient quality of life is a major concern. It is important for the physician and patient to discuss the various treatment options; patient preference for either vigorous treatment or no treatment should be respected. In presenting treatment options, physiological status, not chronological age, should influence the physician's treatment suggestions. The patient should not be given unrealistic expectations. Appropriate psychological support is an important component of care and patients must receive this. In addition, research should be conducted to determine whether psychological factors affect prognosis, response, and survival.

In patients with refractory ovarian cancer there is no indication for the use of high-dose chemotherapy followed by bone marrow or peripheral blood stem cell rescue other than in the setting of clinical trials.

What Are Important Directions for Future Research?

- Currently available imaging techniques and tumor markers should be utilized in clinical trials to determine whether ovarian cancer can be identified at an earlier stage, whether this can reduce mortality from ovarian cancer, and whether this can be done without increasing morbidity and mortality for those women who have abnormal screening results but do not have ovarian cancer. Study of this question should include both pre- and postmenopausal women.
- New serum markers (e.g., OVX-1, M-CSF) and imaging techniques should be investigated to see if a more sensitive and specific panel of screening parameters can be identified.
- Researchers should more clearly evaluate and quantitate the benefits of currently used oral contraceptives in reducing the risk of ovarian cancer, evaluate the necessary duration of use and the benefits of prolonged use, and evaluate the other benefits and risks and long-term outcome.
- A national serum and tissue bank should be established.
- Identification of women at increased risk for ovarian cancer should be improved. Studies should focus on genetic research, such as BRCA-1. In addition, environmental and epidemiologic research should be continued.
- The safety and efficacy of laparoscopy for women with ovarian cancer should be studied.
- The combination of platinum compounds and paclitaxel should be further investigated in earlier stage disease. In addition, the ideal dose and schedule of paclitaxel must be evaluated in clinical trials.
- A prospective randomized study is needed to identify optimal treatment of various subsets of stage I ovarian cancer.
- Whole abdominal radiation should be reevaluated and newer radiation techniques evaluated in the treatment of optimally debulked stage II and III disease.

- Innovative approaches to the treatment of advanced primary as well as recurrent ovarian cancer must be identified and studied. Examples include new molecular targets, agents to overcome resistance, and drugs that inhibit signal transduction pathways.
- Clinical trials exploring the role of consolidation therapy in patients with a complete response to primary therapy should be given high priority.
- Measures of the quality of life in women with ovarian cancer must be identified, evaluated, and then utilized in optimizing the care of patients.

Conclusions

Although the number of women dying from ovarian cancer in the United States has continued to rise, the application of available recent information may be able to contribute to the reduction in incidence of and morbidity and mortality from this disease.

- The risk of ovarian cancer can be reduced by the use of oral contraceptives. However, the other risks and benefits of the birth control pill must be considered.
- Women who have no family members with ovarian cancer have a 1 in 70 lifetime risk of developing the disease. Women who have one first-degree relative with ovarian cancer have a 5 percent risk, and women with two first-degree relatives have a 7 percent risk. A very small subset of these women (3 percent of the women with two relatives) have an autosomal dominant syndrome with 80 percent penetrance, which places them at very high risk for ovarian cancer. The three known hereditary syndromes that may place a women at exceedingly high risk are familial site-specific ovarian cancer syndrome, breast-ovarian cancer syndrome, and Lynch syndrome II .
- All women should have a careful family history taken by their primary care physician. Women who are presumed to have one of the syndromes mentioned above, which would place them at exceedingly high risk, should have at least an annual physical exam and a bimanual recto-vaginal examination, CA 125 determinations, and TVS. When childbearing is completed, or at least by age 35, prophylactic bilateral oophorectomy is recommended.
- There is no evidence available yet that the current screening modalities of CA 125 and TVS can be effectively used for widespread screening to reduce mortality from ovarian cancer nor that their use will result in decreased rather than increased morbidity and mortality. Routine screening has resulted in unnecessary surgery with its attendant potential risks. Clearly, it is important to identify and validate effective screening modalities. Currently available technology for screening should be

employed in the context of clinical trials to determine the efficacy of these modalities and their impact upon ovarian cancer mortality. In addition, research must be continued to identify additional markers and imaging techniques that will be useful. If a woman has one first-degree relative with ovarian cancer (making her lifetime risk of developing the disease 5 percent) but no clinical trials are available to her, she may feel that despite the absence of prospective data, this is sufficient risk for her to be screened. This alternative and opportunity should be available to the woman and her physician.

- If a woman is undergoing pelvic surgery, removal of her ovaries at that time will almost fully eliminate her risk of ovarian cancer (although there remains a minimal risk of peritoneal carcinomatosis). If the woman is premenopausal, discussion of estrogen replacement therapy is important prior to removal of the ovaries, since for some younger women, if estrogen replacement is not utilized, the risk of premature menopause and the potential for cardiovascular disease and osteoporosis may outweigh the risk of ovarian conservation and the potential for ovarian cancer.
- Although laparoscopic management of the ovarian mass is being utilized, there is no current evidence that if the mass is malignant the patient's opportunity for cure is comparable to that with a more traditional approach. Studies should be done to evaluate the risks and benefits of laparoscopic surgery for these women.
- Women with ovarian masses who have been identified preoperatively as having a significant risk of ovarian cancer should be given the option of having their surgery performed by a gynecologic oncologist.
- Aggressive attempts at cytoreductive surgery as the primary management of ovarian cancer will improve the patient's opportunity for long-term survival.
- Women with stage IA grade 1 and most IB grade 1 ovarian cancer do not require postoperative adjuvant therapy. Many remaining stage I patients do require

adjuvant therapy. Subsets of stage I must be fully defined and ideal treatment determined.

- Women with stages II, III, and IV epithelial ovarian cancer (other than LMP tumors) should receive postoperative chemotherapy.
- One American study concludes that platinum and paclitaxel are the optimal first-line chemotherapy following primary debulking surgery, and most oncologists in the United States are using this regimen. No consensus could be reached on unqualified endorsement of this recommendation pending maturation of the data.
- Second-look laparotomy should be done only for patients on clinical trials or for those patients in whom the surgery will affect clinical decisionmaking and clinical course. It should not be employed as routine care for all patients.
- For women who have completed primary therapy for ovarian cancer there is no evidence regarding ideal followup. Studies are needed to identify additional second-line therapies and to define how they can best be utilized to prolong survival, improve quality of life, and potentially provide the possibility for cure. Clearly, women with a symptomatic recurrence should receive whatever modalities will improve their symptoms and quality of life.
- For a woman with recurrent ovarian cancer resistant to platinum who has not received paclitaxel, paclitaxel is the best salvage therapy currently available.
- Physicians must be encouraged to discuss clinical trial participation with women, and women should be encouraged to participate.
- All women should have access to accurate and complete information regarding ovarian cancer. Furthermore, there must be no barriers to women's access to qualified specialists, optimal therapy, and protocols.

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OVARIAN CANCER: Screening, Treatment, and Followup

*A Continuing Medical Education Activity
Sponsored by the
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OBJECTIVE

The objective of this NIH Consensus Statement is to inform the biomedical research and clinical practice communities of the results of the NIH Consensus Development Conference on Ovarian Cancer: Screening, Treatment, and Followup. The statement provides state-of-the-art information regarding screening, prevention, diagnosis, and treatment of ovarian cancer, and it presents the conclusions and recommendations of the consensus panel regarding these issues. In addition, the statement identifies those areas of study that deserve further investigation. Upon completion of this educational activity, the reader should possess a clear working knowledge of the state-of-the-art regarding screening, prevention, diagnosis, and treatment of ovarian cancer.

ACCREDITATION

The National Institutes of Health is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. The National Institutes of Health designates this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association.

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INSTRUCTIONS: The consensus statement contains the correct answers to the following 14 questions. Select your answer to each question and write the corresponding letter in the answer space provided. Mail the completed test **no later than December 31, 1995**, to the address shown on the last page of this test. You will receive notification of your test results within 2 to 3 weeks. If you have successfully completed the test (10 or more correct), you will receive a certificate for 1 hour of CME credit along with your test results. Photocopies of this form are acceptable.

1. Ovarian cancer is the leading cause of deaths from gynecologic malignancies in the United States. In 1994, it is estimated that the following numbers of new cases and deaths will occur:
- a) 183,000 new cases; 46,000 deaths
 - b) 31,000 new cases; 5,900 deaths
 - c) 24,000 new cases; 13,600 deaths
 - d) 1,500 new cases; 4,600 deaths

ANSWER: _____

2. Most women with early ovarian cancer have the following symptoms:
- a) severe gastrointestinal discomfort
 - b) pelvic pressure and sensation of a mass
 - c) abnormal vaginal bleeding
 - d) no symptoms, or mild and nonspecific symptoms

ANSWER: _____

3. Hereditary ovarian cancer syndromes (breast-ovarian syndrome, site-specific ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome [Lynch syndrome II, Cancer Family Syndrome]) account for:
- a) 50% of ovarian cancers
 - b) 25% of ovarian cancers
 - c) 10% of ovarian cancers
 - d) less than 5% of ovarian cancers

ANSWER: _____

4. Serum CA 125 has specific specificity, sensitivity, and positive predictive value to make it an adequate screening test for ovarian cancer.
- a) true
 - b) false

ANSWER: _____

5. All women over age 35 should be screened for ovarian cancer with CA 125 and transvaginal ultrasound every 6 months.
- a) true
 - b) false

ANSWER: _____

6. Factors protective against the development of ovarian cancer include:
- a) more than one full-term pregnancy
 - b) use of oral contraceptives
 - c) breast-feeding
 - d) all of the above

ANSWER: _____

7. Management of an adnexal mass should be based on the following factors:
- a) age and menopausal status of the patient
 - b) size of the mass
 - c) ultrasonographic features of the mass
 - d) level of serum CA 125
 - e) all of the above

ANSWER: _____

8. Laparoscopy has been proven safe and effective in the management of adnexal masses suspicious for ovarian malignancies.
- a) true
 - b) false

ANSWER: _____

9. Conservative surgery, as defined by that preserving reproductive tissue (uterus, contralateral ovary), may be appropriate in some young women with early-stage ovarian cancer.
- a) true
 - b) false

ANSWER: _____

10. All patients with ovarian tumors of low malignant potential should receive adjuvant chemotherapy or radiotherapy after primary surgical treatment.
- a) true
 - b) false

ANSWER: _____

11. Factors predicting longer survival in patients with ovarian cancer include the following:
- a) younger age
 - b) early stage
 - c) low tumor grade
 - d) low residual tumor volume
 - e) all of the above

ANSWER: _____

12. In patients with advanced ovarian cancer, chemotherapy is most effective in patients who have undergone maximal (optimal) cytoreduction or who present with a low volume of disease.
- a) true
 - b) false

ANSWER: _____

13. Women who have no family members with ovarian cancer have the following lifetime risk of ovarian cancer:
- a) 1/9
 - b) 1/25
 - c) 1/70
 - d) 1/150

ANSWER: _____

14. The following chemotherapy agents have been proven effective in patients with ovarian cancer:
- a) cisplatin
 - b) carboplatin
 - c) paclitaxel (Taxol)
 - d) cyclophosphamide
 - e) all of the above

ANSWER: _____

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